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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/288,837	04/08/1999	GENE H. MACDONALD	5470-238	7924

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EXAMINER
BRUMBACK, BRENDA G

ART UNIT	PAPER NUMBER
1642	21

DATE MAILED: 11/26/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/288,837	Applicant(s) MACDONALD ET AL.	
	Examiner Brenda G. Brumback	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *84,85,90-93 and 95-102* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84,85,90-93 and 95-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/02/2001 has been entered (Paper # 20).

2. Claims 84 and 95 were amended. Claims 84-85, 89-93, and 96-102 are pending and under examination.

Claim Rejections - 35 USC § 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The rejection of claims 84, 85, 90-93, and 95-102 under 35 U.S.C. 103(a) as being unpatentable over Johnston et al. in view of Falo Jr. et al. is withdrawn. Applicant's arguments and the Olmsted Declaration were persuasive.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112

4. Claims 84, 85, 90-93, and 95-102 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims recite a composition comprising infectious alphavirus particles in an immunogenically effective amount ... said composition effective to treat a cancer cell expressing said native cancer antigen. While the specification discloses administration of the claimed alphavirus particles in an amount effective to induce an active immune response (see the sentence bridging pages 14-15), it is unclear whether "an immunogenically effective amount" is that amount required to elicit any amount of immunogenic response to the antigen expressed by the alphavirus particle or whether "an immunogenically effective amount" is that amount required for eliciting an immunogenic response of sufficient magnitude to elicit a therapeutic effect to treat a cancer cell. Absent specific teachings in the disclosure, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

The instant claims recite a "native cancer cell antigen". The specification discloses a native cancer cell antigen both as any naturally-occurring cancer cell antigen (see page 7, line 6, and page 17, line 31, through page 18, line 4) and as an antigen specifically expressed by the recipient's cancer cells (see page 9, line 32). It is thus unclear if a native antigen is intended to encompass only an antigen expressed by the recipient of the claimed composition or if it is

intended to encompass any antigen expressed by any cancer cell. Thus, the metes and bounds of the claimed invention are ambiguous and the claims are indefinite.

The claims recite a T-cell epitope or a B-cell epitope. While the specification teaches immunogenic epitopes as T-cell and B-cell epitopes, it fails to disclose the metes and bounds of such epitopes. Absent such disclosure the claims are indefinite.

5. Claims 84, 85, 90-93, and 95-102 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its

face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: Although the instant claims are indefinite for the reasons outlined *supra*, the claimed invention has been interpreted as drawn to a composition comprising infectious alphavirus particles comprising one or more native cancer cell antigens in an immunologically effective amount to treat a cancer cell expressing the native cancer cell antigen.

The state of the prior art and the predictability or lack thereof in the art: Applicant's claims encompass the experimental and unpredictable field of *in vivo* cancer therapy in humans and other mammals. Jain (Cancer and Metastasis Reviews 9:253-266, 1990) teaches that the efficacy of cancer therapeutics, and therapeutic antibodies in particular, has been limited by the inability of the antibodies to reach target tumor sites *in vivo* in adequate quantities to elicit a therapeutic effect (see the abstract). Jain teaches that due to the heterogenicity of the blood

supply to tumors, elevated interstitial pressure, large transport distances in the interstitium, and the increased time for slowly moving macromolecules, such as antibodies, to reach distal regions of a tumor, the efficacy of antibody therapy *in vivo* is limited and extremely unpredictable (see the abstract). Although Jain primarily addresses administration of antibodies made extra corporally, rather than generation of the antibodies in the patient, conventional wisdom would dictate that antibodies generated in the patient would encounter the same barriers as antibodies which are made extra corporally and subsequently administered to the patient.

The amount of direction or guidance present and the presence or absence of working examples: The specification teaches how to make the claimed alphavirus vectors and how to transfect a tumor cell line to express an artificial cancer antigen (influenza hemagglutinin antigen) (see page 21-28, Examples 1-10). There is no guidance as to how to make or administer infectious alphavirus expressing a native cancer antigen so as to induce an immune response against cancer cells expressing only native antigens. There is no guidance as to how to administer the claimed compositions *in vivo* so as to overcome the teachings of unpredictability found in the art regarding ineffectiveness of antibodies in reaching target tumor sites. The specification teaches reduction of xenografted tumors in a mouse model. However, the art teaches that the mouse xenograft model is an inadequate model for predicting *in vivo* therapeutic efficacy for cancer. Osband et al. (Immunology Today, 11/6:193-195) teach that many immunotherapeutic agents are inactive in other species and that owing to the extreme complexity of the host-tumor immunorelationship, animal models do not fully mimic the biology of human

patients with cancer (see especially the paragraph bridging pages 193-194). Gura (Science 278:1041-1042, 1997) teaches that xenograft tumors in mice don't behave like naturally occurring tumors in humans and that therapeutics which appear to be effective in the xenograft model often work poorly in humans (see page 1041, the entire document and especially column 2, last full paragraph). The specification fails to provide any guidance or teachings as to how to overcome these teachings of unpredictability regarding the ineffectiveness of the mouse xenograft model for predicting therapeutic effectiveness in humans.

The breadth of the claims and the quantity of experimentation needed: Because of the teachings of unpredictability regarding *in vivo* therapy for cancer in humans and in other mammals and because the specification fails to contain teachings sufficient to overcome the teachings of unpredictability found in the art, it would require undue experimentation by one of skill in the art to be able to make and use the claimed compositions.

Conclusion

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone

number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1642 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

BB
November 15, 2001

Brenda Brumback
Brenda Brumback,
Patent Examiner